Molecular Dynamics Simulation for Proteins : GROMACS Tutorial

분자동역학 모의실험 튜토리얼

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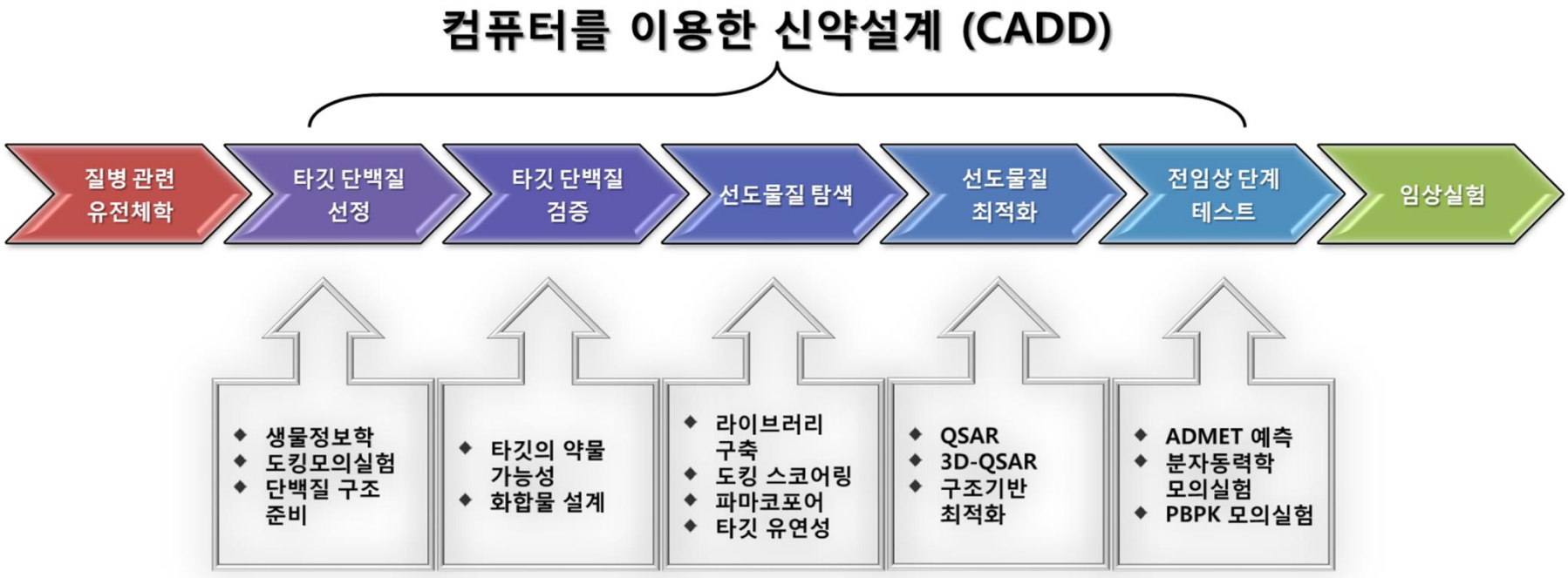
Computer-Aided Drug Design (CADD) and Molecular Modeling



- 합리적 분자설계를 수행하기 위해서 컴퓨터를 이용한 신약설계 방법 (CADD)이 사용되고 있으며, 이러한 in silico 접근법은 리간드기반 신약설계 (ligand-based drug design)와 구조기반 신약설계 (structure-based drug design)으로 구분된다.

Molecular Dynamics (MD) simulation in CADD

Molecular modeling study on Target protein

- **Molecular dynamics (MD) simulation study** for mechanism of target protein and for further finding multi-step targeting drug.
- **Molecular docking calculation** using known inhibitors to understand reaction mechanism of the protein.

Computer-Aided Drug Design (CADD) for target protein inhibitor

- **Ligand-based and receptor-based pharmacophore modeling** for target protein.
- **Virtual screening** to find target inhibitor candidate molecules.

Refinement and optimization of new inhibitor

- **ADME/Tox and molecular docking** to refine the candidate molecules.
- **MD simulation study** of target protein with inhibitors to optimize the structure.

Identification of target drug candidates

분자동역학 모의실험을 통한 단백질의 실시간 움직임 관찰

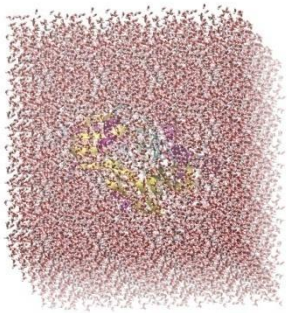
분자동역학 모의실험이란?

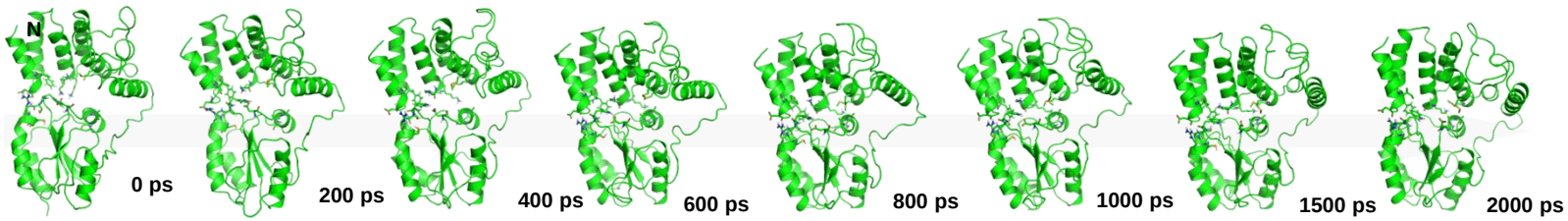
물리화학 법칙을 사용한 계산을 통하여 단백질과 같은 분자들의 실시간 움직임을 자세하게 관찰할 수 있게 해주는 이론적인 실험입니다.

모의실험을 위해 사용되는 슈퍼컴퓨터

슈퍼컴퓨터는 과학기술연산에 사용되는 초고속 컴퓨터입니다. 이러한 컴퓨터의 발달이 복잡한 단백질 구조의 분자동역학 모의실험을 가능하게 했습니다.

분자동역학 모의실험 결과 trajectory: 시간이 흐름에 따른 구조 변화 관찰





- MD는 미시적인 세계를 해석하는데 있어서의 이론의 한계, 실험의 한계를 극복하기 위해 사용되는 방법이다.
- 이러한 계산을 통해서 분자시스템의 화학반응 메커니즘 분석 및 시간에 따른 물성을 조사하는 것을 목표로 한다.
- 실험을 하는 것이 힘들거나 불가능한 경우 system의 성질을 알기 위해서 (실험적으로 접근 불가능한 조건이나 물질도 구현할 수 있으며, 관측하기 어려운 property들도 얻을 수 있다.)

컴퓨터 모의실험 분야

A. Dynamics Simulations(동력학 모의실험):

1. Molecular Dynamics (MD) Simulation:
   CHARMM, AMBER, GROMACS, NWChem, NAMD, DISCOVER,..
2. Langevin Dynamics (LD) Simulation:
   CHARMM, NAMD
3. Brownian Dynamics (BD) Simulation:
   UHBD (University of Houston BD)

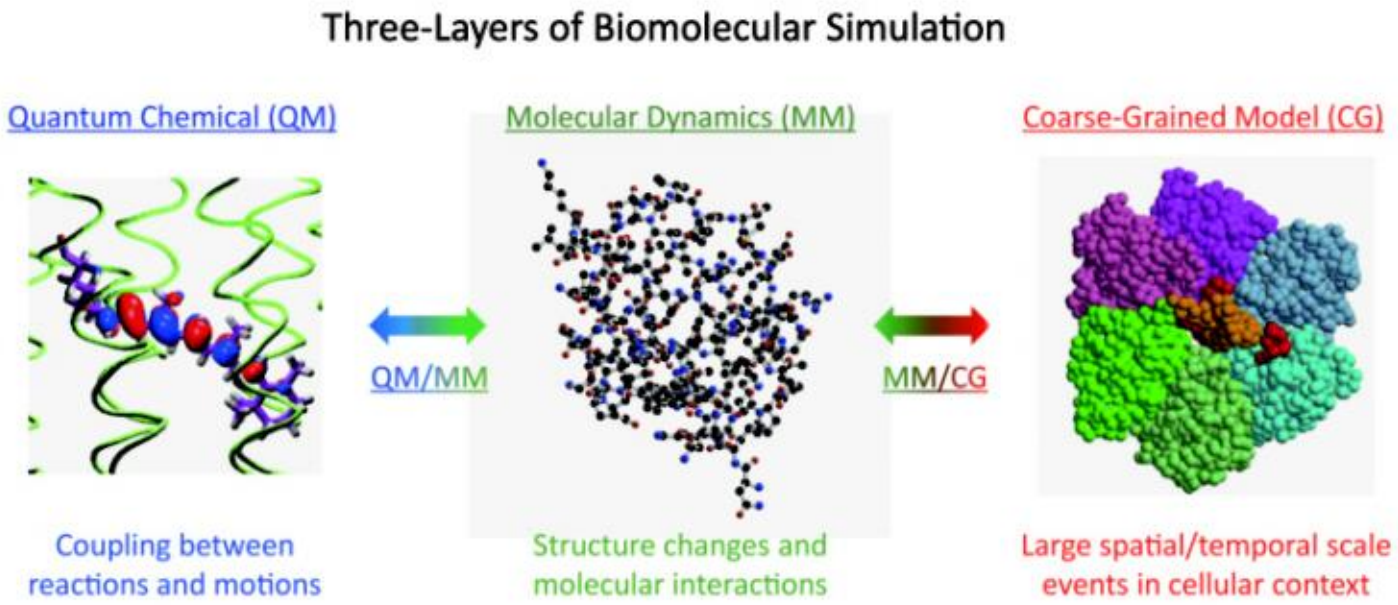


그림 출처 http://www.riken.jp/csrp-mol/research.html

GROMACS: FAST, FLEXIBLE, FREE

- 분자동역학 모의실험을 하기 위한 도구들로 CHARMM, NAMD, Discover, **GROMACS**, 등 여러가지 프로그램들이 있지만, 그 중에서도 **GROMACS**는 GNU정신에 입각하여 공짜로 다운받을 수 있고, 계산이 빠르고, 다양한 분석이 가능합니다.

- 또, 수 백에서 수백만의 입자를 갖는 시스템들에서 뉴턴 운동방정식을 계산할 수 있을 정도로 분자동역학을 수행하는데 있어 다재다능한 패키지입니다.

- 이 소프트웨어는 최초로 복잡한 공유결합 상호작용들을 가진 지질과 단백질과 같은 생화학적 분자들을 위해 개발되었지만, 비공유결합 상호작용들을 계산하는데 있어 매우 빠르기 때문에 많은 그룹들이 비생물학적 시스템들에서도 사용하고 있습니다. 예. polyemrs

- **GROMACS**는 현대 분자동역학 도구에서 기대되는 모든 유용한 알고리즘들을 지원할 뿐만 아니라 몇몇 매우 특별한 점들도 가지고 있어 다른 프로그램들과 구별됩니다.

The global MD algorithm

1. Input initial conditions

Potential interaction V as a function of atom positions
Positions $\boldsymbol{r}$ of all atoms in the system
Velocities $\boldsymbol{v}$ of all atoms in the system

$\Downarrow$

repeat 2,3,4 for the required number of steps:

2. Compute forces

The force on any atom

$$\boldsymbol{F}_i = -\frac{\partial V}{\partial \boldsymbol{r}_i}$$

is computed by calculating the force between non-bonded atom pairs:

$$\boldsymbol{F}_i = \sum_j \boldsymbol{F}_{ij}$$

plus the forces due to bonded interactions (which may depend on 1, 2, 3, or 4 atoms), plus restraining and/or external forces.
The potential and kinetic energies and the pressure tensor are computed.

$\Downarrow$

3. Update configuration

The movement of the atoms is simulated by numerically solving Newton's equations of motion

$$\frac{\mathrm{d}^2\boldsymbol{r}_i}{\mathrm{d}t^2} = \frac{\boldsymbol{F}_i}{m_i}$$

or

$$\frac{\mathrm{d}\boldsymbol{r}_i}{\mathrm{d}t} = \boldsymbol{v}_i; \quad \frac{\mathrm{d}\boldsymbol{v}_i}{\mathrm{d}t} = \frac{\boldsymbol{F}_i}{m_i}$$

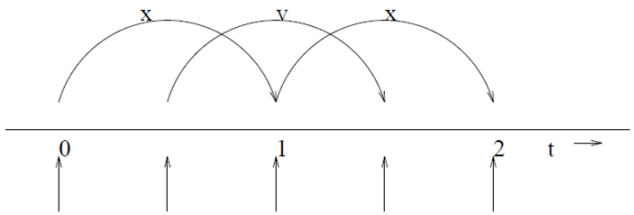
$\Downarrow$

4. if required: **Output step**
write positions, velocities, energies, temperature, pressure, etc.

Energy terms of force field

$$\begin{aligned} E(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N) &= \sum_{bonds} \frac{1}{2} k_i^b (d_i - d_i^0)^2 \\ &+ \sum_{angles} \frac{1}{2} k_i^\theta (\theta_i - \theta_i^0)^2 \\ &+ \sum_{torsions} k_i^\phi [1 + \cos(n_i \phi_i - \delta_i)] \\ &+ \frac{1}{2} \sum_{nonbond} \left(\epsilon_{ij}^{min} \left[\left(\frac{d_{ij}^{min}}{d_{ij}} \right)^{12} - 2 \left(\frac{d_{ij}^{min}}{d_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\epsilon d_{ij}} \right) \end{aligned}$$

Integrating the equation of motion

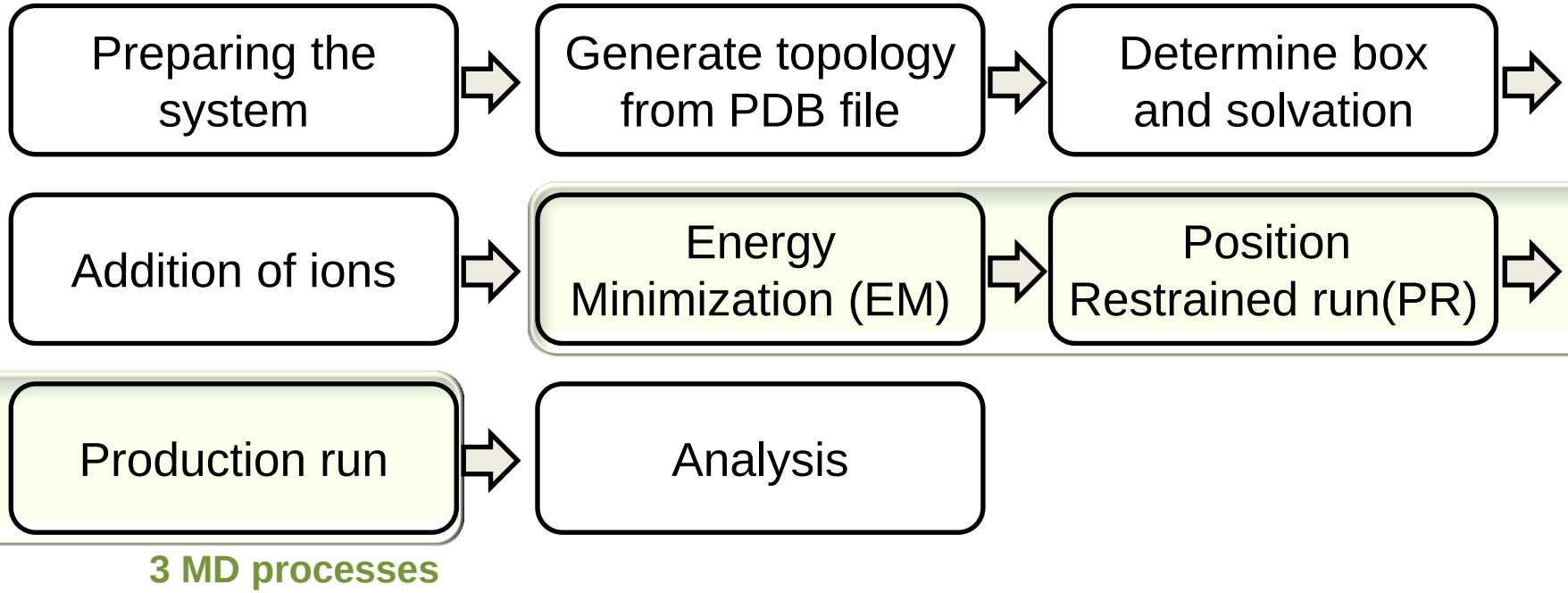


The **Leap-Frog integration** method. The algorithm is called Leap-Frog because r and v are leaping like frogs over each other's backs.

$$\begin{aligned} \boldsymbol{v}(t + \tfrac{1}{2}\Delta t) &= \boldsymbol{v}(t - \tfrac{1}{2}\Delta t) + \frac{\Delta t}{m} \boldsymbol{F}(t) \\ \boldsymbol{r}(t + \Delta t) &= \boldsymbol{r}(t) + \Delta t \boldsymbol{v}(t + \tfrac{1}{2}\Delta t) \end{aligned}$$

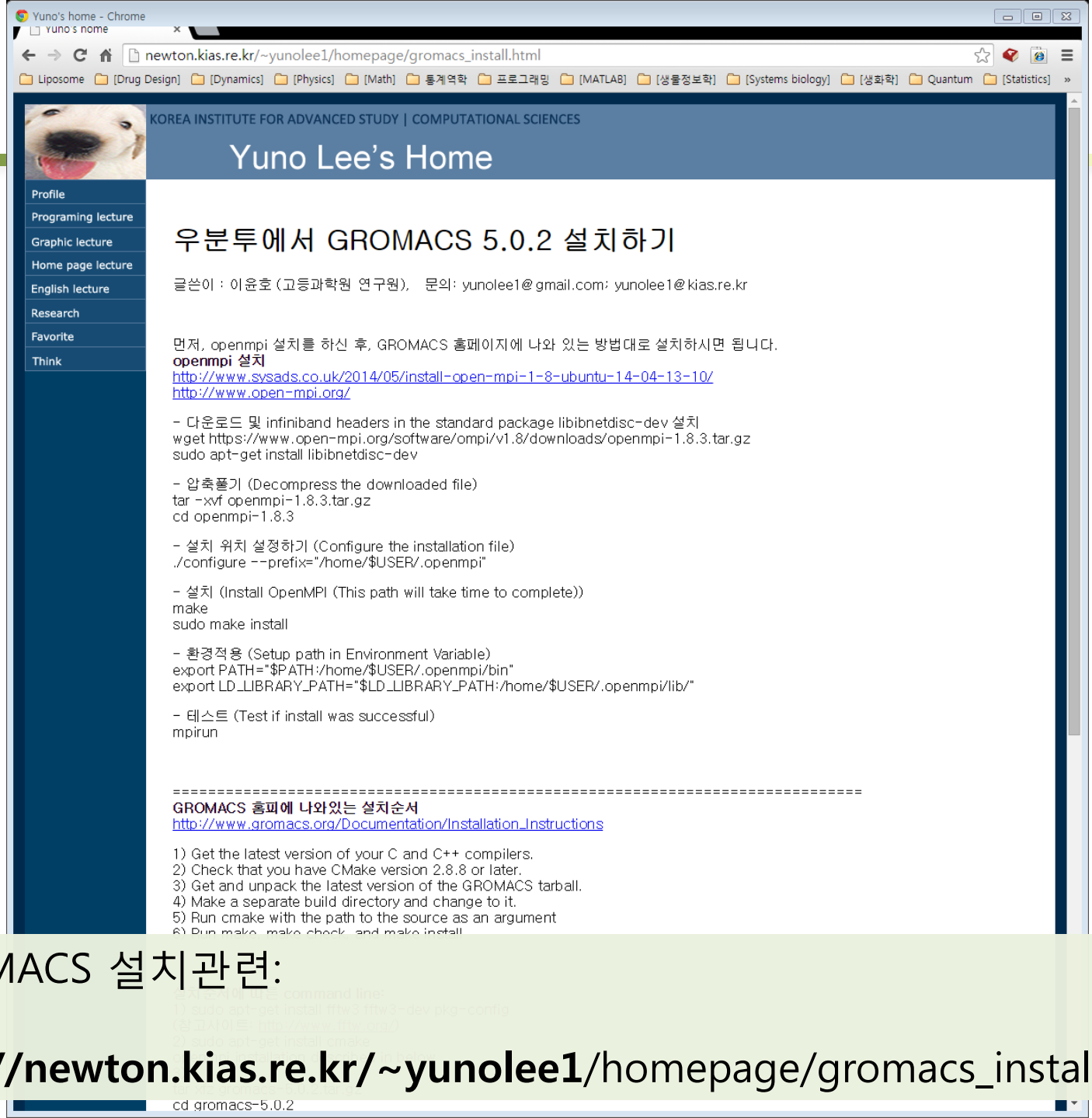
Molecular Dynamics (MD) simulation

Flow chart of MD simulation procedures



GROMACS 설치관련:

http://newton.kias.re.kr/~yunolee1/homepage/gromacs_install.html



GROMACS 설치관련:

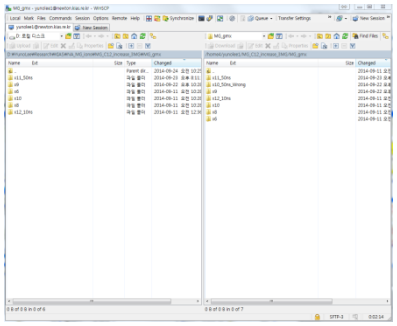
http://newton.kias.re.kr/~yunolee1/homepage/gromacs_install.html

http://cafe.naver.com/insilico (네이버 카페 인실리코)

SSH / SCP (Window OS)

Download PuTTY

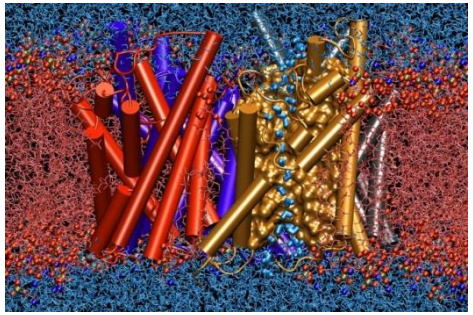
- PuTTY is an SSH and telnet client, developed originally by Simon Tatham for the Windows platform. PuTTY is open source software that is available with source code and is developed and supported by a group of volunteers.
- You can download PuTTY: http://www.chiark.greenend.org.uk/~sgtatham/putty/download.html



Download WinSCP

- WinSCP is an open source free SFTP client, FTP client, WebDAV client and SCP client for Windows. Its main function is file transfer between a local and a remote computer. Beyond this, WinSCP offers scripting and basic file manager functionality.
- You can download WinSCP: http://winscp.net/eng/download.php

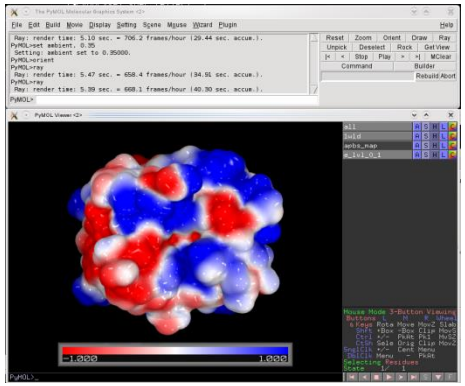
Visualizations – VMD, PyMOL



Download VMD

- VMD is a molecular visualization program for displaying, animating, and analyzing large biomolecular systems using 3-D graphics and built-in scripting. VMD supports computers running MacOS X, Unix, or Windows, is distributed free of charge, and includes source code.

- You can download VMD: http://www.ks.uiuc.edu/Development/Download/download.cgi?PackageName=VMD



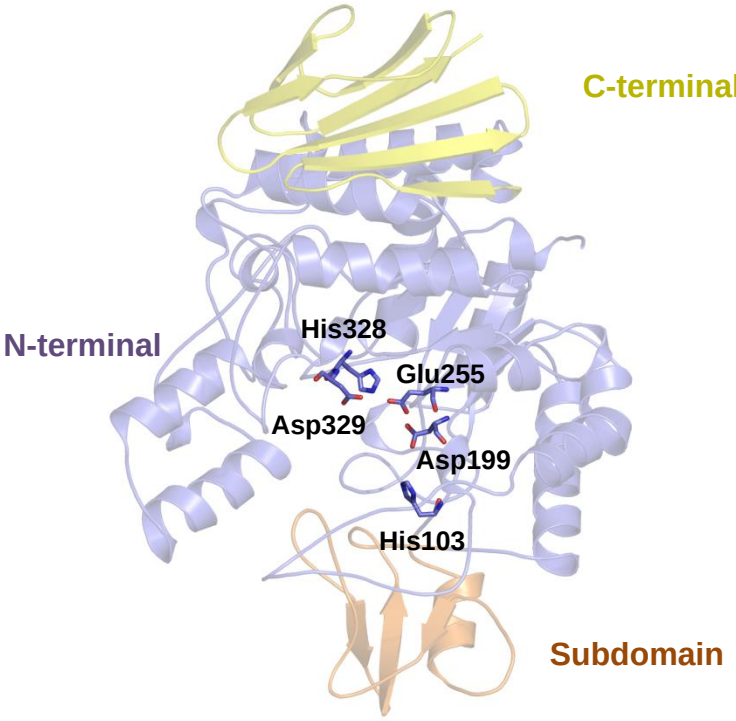
Download PyMOL

- PyMOL is a user-sponsored molecular visualization system on an open-source foundation, maintained and distributed by Schrödinger.

- You can download PyMOL: http://pymol.org/educational/

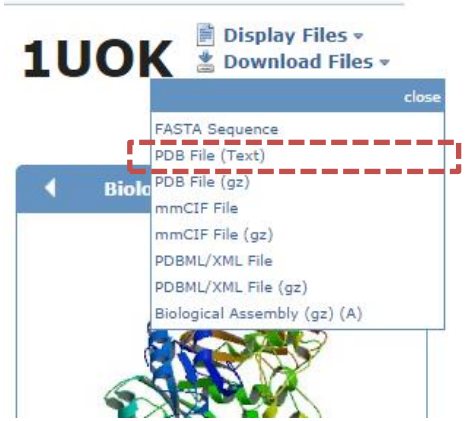
Preparing the system: Crystal structure of α-glucosidase from *B. cereus* (PDBID: 1UOK)

Crystal structure of *B. cereus* α-glucosidase



PDB ID: 1UOK (*B. cereus*)
Resolution: 2.0 Å

"Catalytic triad residues: Asp214, Glu276, Asp349"



- Download the PDB 1UOK from RCSB website(http://www.rcsb.org)
- Delete crystal water molecules using plain text editor such as vi, emacs for Linux; and AcroEdit for Windows.
- Check missing residues in your pdb file

Generate topology from PDB file

```
pdb2gmx -f pro.pdb -o pro.gro -p pro.top -i pro.itp -ff amber03 -water spce -ignh
```

Input file
pro.pdb = the modified pdb file (1UOK).

Output files
pro.gro = a post-processed structure file.
pro.top = the topology for the molecule.
pro.itp = a position restraint file.

Options -ff: force field selection.
-ignh: Ignore H atoms in the PDB file.

Total charge -39.000 e

pro.gro

```
OLIGO-1,6-GLUCOSIDASE
 9068
   1MET     N    1   4.039   4.973  -0.502
   1MET    H1    2   4.106   5.047  -0.499
   1MET    H2    3   4.015   4.946  -0.408
```

pro.top

```
[ molecules ]
; Compound        #mols
Protein_chain_A     1
```

pro.itp

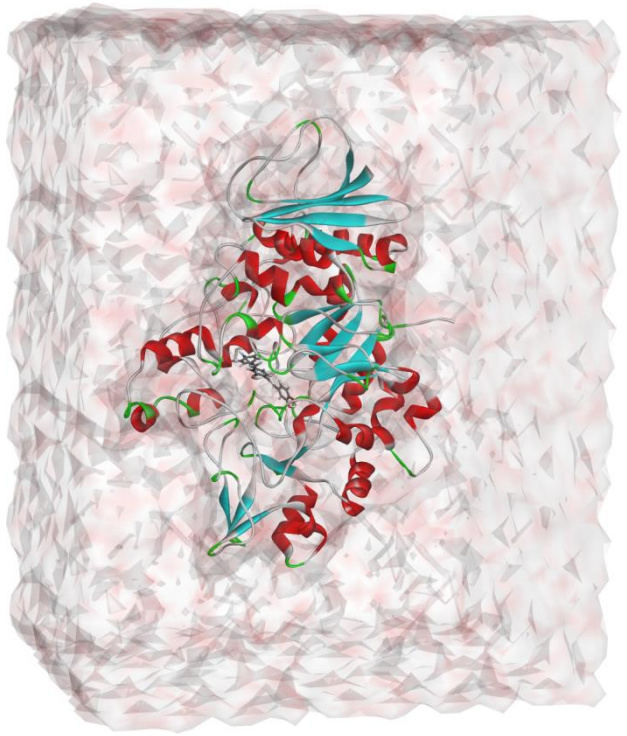
```
[ position_restraints ]
; atom  type      fx      fy      fz
     1     1  1000  1000  1000
     5     1  1000  1000  1000
     7     1  1000  1000  1000
```

Determine box and solvation

```
editconf -f pro.gro -o prob.gro -d 1.2
```

Option -bt: box type (triclinic, cubic, dodecahedron)

```
genbox -cp prob.gro -cs spc216.gro -o b4em.gro -p pro.top
```



Orthorhombic box (1.2 nm from protein edges)

After editconf command,

```
Read 9068 atoms
Volume: 1169.88 nm^3, corresponds to roughly 526400
electrons
No velocities found
    system size :  5.835  7.565  6.374 (nm)
    center      :  5.529  4.228  1.140 (nm)
    box vectors : 10.610 10.610 12.000 (nm)
    box angles  :  90.00  90.00 120.00 (degrees)
    box volume  :1169.88               (nm^3)
    shift       : -1.411  0.754  3.247 (nm)
new center      :  4.117  4.982  4.387 (nm)
new box vectors :  8.235  9.965  8.774 (nm)
new box angles  :  90.00  90.00  90.00 (degrees)
new box volume  : 720.01               (nm^3)
```

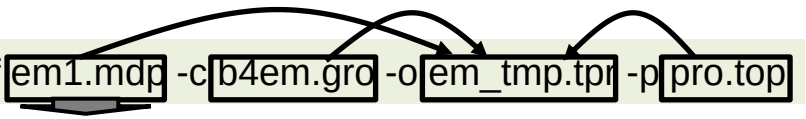
After genbox command,

pro.top

```
[ molecules ]
; Compound       #mols
Protein_chain_A     1
SOL             20930
```

Addition of ions

Total charge -39.000 e (obtained from pdb2gmx)




```
; em1.mdp - used as input into grompp to generate em_tmp.tpr and em1.tpr
; Parameters describing what to do, when to stop and what to save
integrator              = steep         ; Algorithm (steep = steepest descent minimization)
emtol                   = 1000.0        ; Stop minimization when the maximum force < 1000.0 kJ/mol/nm
emstep                  = 0.01          ; Energy step size
nsteps                  = 50000         ; Maximum number of (minimization) steps to perform

; Parameters describing how to find the neighbors of each atom and how to calculate the interactions
nstlist                 = 1             ; Frequency to update the neighbor list and long range forces
ns_type                 = grid          ; Method to determine neighbor list (simple, grid)
rlist                   = 1.0           ; Cut-off for making neighbor list (short range forces)
coulombtype             = PME           ; Treatment of long range electrostatic interactions
rcoulomb                = 1.0           ; Short-range electrostatic cut-off
rvdw                    = 1.0           ; Short-range Van der Waals cut-off
pbc                     = xyz           ; Periodic Boundary Conditions (yes/no)
```

```
genion -s em_tmp.tpr -o ion_add.gro –p pro.top -np 39 -pname NA -nn 0 -nname CL
```

or

```
genion -s em_tmp.tpr -o ion_add.gro -p pro.top -pname NA -nname CL -neutral -conc 0.1
```

pro.top

```
[ molecules ]
; Compound        #mols
Protein_chain_A     1
SOL         20805
NA          82
CL          43
```

Option -conc: Specify salt concentration (mol/liter). This will add sufficient ions to reach up to the specified concentration as computed from the volume of the cell in the input .tpr file.

Energy Minimization (EM)

```
grompp -f em1.mdp -c ion_add.gro -o em1.tpr -p pro.top
```

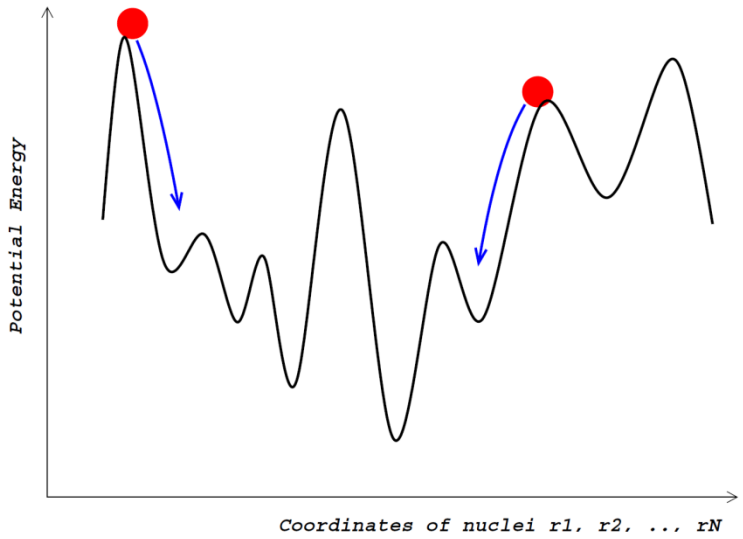
```
mdrun -v -deffnm em1
```

or

```
mpirun -np 12 mdrun -v -s em1.tpr -c after_em1.gro -deffnm em1 >& em1.job
```

Output files
em1.log: Log file of the EM process
em1.edr: Binary energy file
em1.trr: Binary full-precision trajectory
em1.gro: Energy-minimized structure

Algorithms:
Steepest descent, Conjugate gradient



Position Restrained run(PR) - NVT

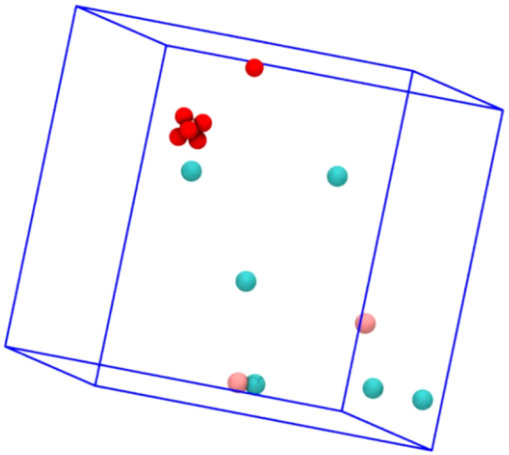
grompp -f pr_NVT.mdp -o pr_NVT.tpr -c after_em1.grc -p pro.top

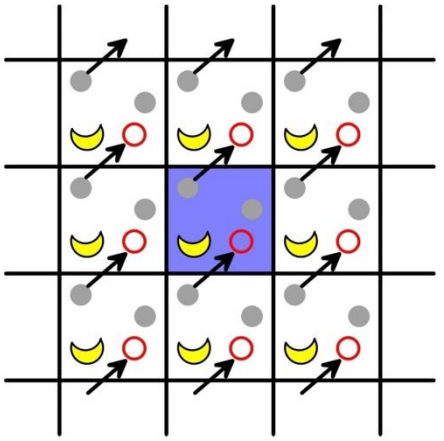
mdrun -v ***-c after_pr_NVT*** -deffnm pr_NVT

title	= NVT equilibration		
define	= -DPOSRES		; position restrain the protein
; Run parameters			
integrator	= md		; leap-frog integrator
nsteps	= 50000		; 2 * 50000 = 100 ps
dt	= 0.002		; 2 fs
; Output control			
nstxout	= 100		; save coordinates every 0.2 ps
nstvout	= 100		; save velocities every 0.2 ps
nstenergy	= 100		; save energies every 0.2 ps
nstlog	= 100		; update log file every 0.2 ps
; Bond parameters			
continuation	= no		; first dynamics run
constraint_algorithm	= lincs		; holonomic constraints
constraints	= all-bonds		; all bonds (even heavy atom-H bonds) constrained
lincs_iter	= 1		; accuracy of LINCS
lincs_order	= 4		; also related to accuracy
; Neighborsearching			
ns_type	= grid		; search neighboring grid cells
nstlist	= 5		; 10 fs
rlist	= 1.0		; short-range neighborlist cutoff (in nm)
rcoulomb	= 1.0		; short-range electrostatic cutoff (in nm)
rvdw	= 1.0		; short-range van der Waals cutoff (in nm)
; Electrostatics			
coulombtype	= PME		; Particle Mesh Ewald for long-range electrostatics
pme_order	= 4		; cubic interpolation
fourierspacing	= 0.16		; grid spacing for FFT
; Temperature coupling is on			
tcoupl	= V-rescale		; modified Berendsen thermostat
tc-grps	= Protein	Non-Protein	; two coupling groups - more accurate
tau_t	= 0.1	0.1	; time constant, in ps
ref_t	= 300	300	; reference temperature, one for each group, in K
; Pressure coupling is off			
pcoupl	= no		; no pressure coupling in NVT
; Periodic boundary conditions			
pbc	= xyz		; 3-D PBC
; Dispersion correction			
DispCorr	= EnerPres		; account for cut-off vdW scheme
; Velocity generation			
gen_vel	= yes		; assign velocities from Maxwell distribution
gen_temp	= 300		; temperature for Maxwell distribution
gen_seed	= -1		; generate a random seed

Canonical (NVT, Helmhotz free-energy)

$\cdot\ T = \sum m \langle v^2 \rangle / (3k_b)$





Position Restrained run(PR) - NPT

grompp -f pr_NPT.mdp -o pr.tpr -c after_pr_NVT.gro -p pro.top

mdrun -v ***-c after_pr*** -deffnm pr

```
title                    = NPT equilibration
define                   = -DPOSRES                          ; position restrain the protein
; Run parameters
integrator               = md                                ; leap-frog integrator
nsteps                   = 50000                             ; 2 * 50000 = 100 ps
dt                       = 0.002                             ; 2 fs
; Output control
nstxout                  = 100                               ; save coordinates every 0.2 ps
nstvout                  = 100                               ; save velocities every 0.2 ps
nstenergy                = 100                               ; save energies every 0.2 ps
nstlog                   = 100                               ; update log file every 0.2 ps
; Bond parameters
continuation             = yes                               ; Restarting after NVT
constraint_algorithm     = lincs                             ; holonomic constraints
constraints              = all-bonds                         ; all bonds (even heavy atom-H bonds) constrained
lincs_iter               = 1                                 ; accuracy of LINCS
lincs_order              = 4                                 ; also related to accuracy
; Neighborsearching
ns_type                  = grid                              ; search neighboring grid cells
nstlist                  = 5                                 ; 10 fs
rlist                    = 1.0                               ; short-range neighborlist cutoff (in nm)
rcoulomb                 = 1.0                               ; short-range electrostatic cutoff (in nm)
rvdw                     = 1.0                               ; short-range van der Waals cutoff (in nm)
; Electrostatics
coulombtype              = PME                               ; Particle Mesh Ewald for long-range electrostatics
pme_order                = 4                                 ; cubic interpolation
fourierspacing           = 0.16                              ; grid spacing for FFT
; Temperature coupling is on
tcoupl                   = V-rescale                         ; modified Berendsen thermostat
tc-grps                  = Protein          Non-Protein      ; two coupling groups - more accurate
tau_t                    = 0.1              0.1              ; time constant, in ps
ref_t                    = 300              300              ; reference temperature, one for each group, in K
; Pressure coupling is on
pcoupl                   = Parrinello-Rahman                 ; Pressure coupling on in NPT
pcoupltype               = isotropic                         ; uniform scaling of box vectors
tau_p                    = 2.0                               ; time constant, in ps
ref_p                    = 1.0                               ; reference pressure, in bar
compressibility          = 4.5e-5                            ; isothermal compressibility of water, bar^-1
refcoord_scaling         = com
; Periodic boundary conditions
pbc                      = xyz                               ; 3-D PBC
; Dispersion correction
DispCorr                 = EnerPres                          ; account for cut-off vdW scheme
; Velocity generation
gen_vel                  = no                                ; Velocity generation is off
```

Isothermal-isobaric (NPT, Gibbs free-energy)

- $P = kinetic + virial\ contributions$

Production run

```
grompp -f md_NPT.mdp -o md1.tpr -c after_pr.gro -p pro.top
```

```
mdrun -v -deffnm md1
```

```
title                    = MD
; Run parameters
integrator               = md                    ; leap-frog integrator
nsteps                   = 500000                ; 2 * 500000 = 1000 ps, 1 ns
dt                       = 0.002                 ; 2 fs
; Output control
nstxout                  = 1000                  ; save coordinates every 2 ps
nstvout                  = 1000                  ; save velocities every 2 ps
nstxtcout                = 1000                  ; xtc compressed trajectory output every 2 ps
nstenergy                = 1000                  ; save energies every 2 ps
nstlog                   = 1000                  ; update log file every 2 ps
; Bond parameters
continuation             = yes                   ; Restarting after NPT
constraint_algorithm     = lincs                 ; holonomic constraints
constraints              = all-bonds             ; all bonds (even heavy atom-H bonds) constrained
lincs_iter               = 1                     ; accuracy of LINCS
lincs_order              = 4                     ; also related to accuracy
; Neighborsearching
ns_type                  = grid                  ; search neighboring grid cells
nstlist                  = 5                     ; 10 fs
rlist                    = 1.0                   ; short-range neighborlist cutoff (in nm)
rcoulomb                 = 1.0                   ; short-range electrostatic cutoff (in nm)
rvdw                     = 1.0                   ; short-range van der Waals cutoff (in nm)
; Electrostatics
coulombtype              = PME                   ; Particle Mesh Ewald for long-range electrostatics
pme_order                = 4                     ; cubic interpolation
fourierspacing           = 0.16                  ; grid spacing for FFT
; Temperature coupling is on
tcoupl                   = V-rescale             ; modified Berendsen thermostat
tc-grps                  = Protein  Non-Protein  ; two coupling groups - more accurate
tau_t                    = 0.1      0.1          ; time constant, in ps
ref_t                    = 300      300          ; reference temperature, one for each group, in K
; Pressure coupling is on
pcoupl                   = Parrinello-Rahman     ; Pressure coupling on in NPT
pcoupltype               = isotropic             ; uniform scaling of box vectors
tau_p                    = 2.0                   ; time constant, in ps
ref_p                    = 1.0                   ; reference pressure, in bar
compressibility          = 4.5e-5                ; isothermal compressibility of water, bar^-1
; Periodic boundary conditions
pbc                      = xyz                   ; 3-D PBC
; Dispersion correction
DispCorr                 = EnerPres              ; account for cut-off vdW scheme
; Velocity generation
gen_vel                  = no                    ; Velocity generation is off
```

Check after grompp command

Estimate for the relative computational load of the PME mesh part: 0.25

For rectangular boxes the optimal particle-particle(PP) to PME node ratio is usually 3:1, for rhombic dodecahedra usually 2:1.

Analysis

- Check trajectory using VMD program

make_ndx -f md1.tpr -o in_md1.ndx (except for water molecule)

editconf -f after_pr.gro -n in_md1.ndx -o **after_pr.pdb** (pdb file contained only protein)

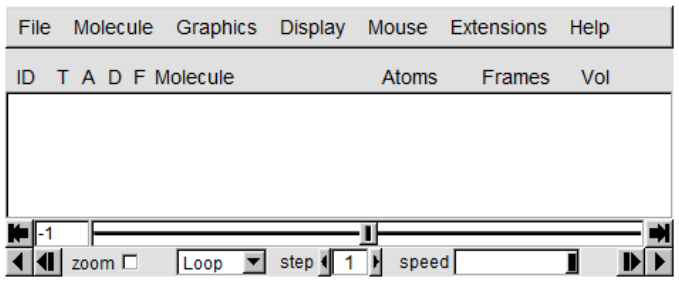
trjconv -f md1.xtc -s md1.tpr -n in_md1.ndx -o **trajout.xtc** -pbc nojump

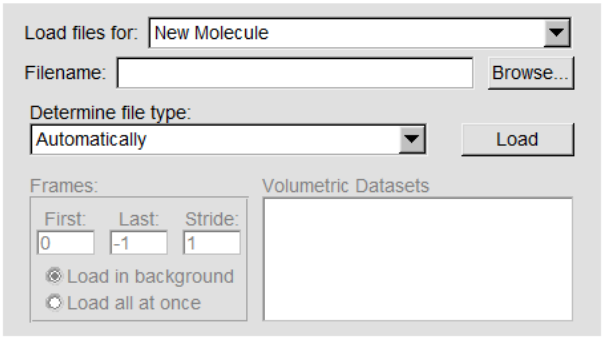
Option -pbc nojump: to remove PBC jumping effect in trajectory
-dt: Only write frame when t MOD dt = first time (ps)
it is possible to reduce the number of frames in the output.

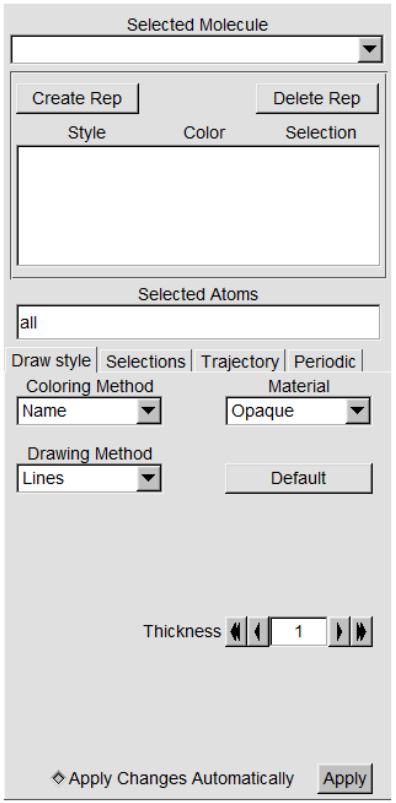
Transfer **after_pr.pdb** and **trajout.xtc** files from Linux server to Window PC

In VMD program,
File -> New Molecule... -> Browse... -> select **after_pr.pdb** -> Load
Select **trajout.xtc** -> Load (should keep Load files for: 0: after_pr.pdb)

Graphics -> Representations...







Analysis

- RMSD, RMSF, Radius of Gyration, Energy, Distance, H-bond Measure

RMSD (Root Mean Square Deviation)
g_rms -f md1.xtc -s after_pr.pdb -o Ca_RMSD.xvg
-> C alpha to C alpha

RMSF (Root Mean Square Fluctuation)
g_rmsf -f md1.xtc -s md1.tpr -n in_md1.ndx -o Ca_RMSF.xvg
-> C alpha to C alpha

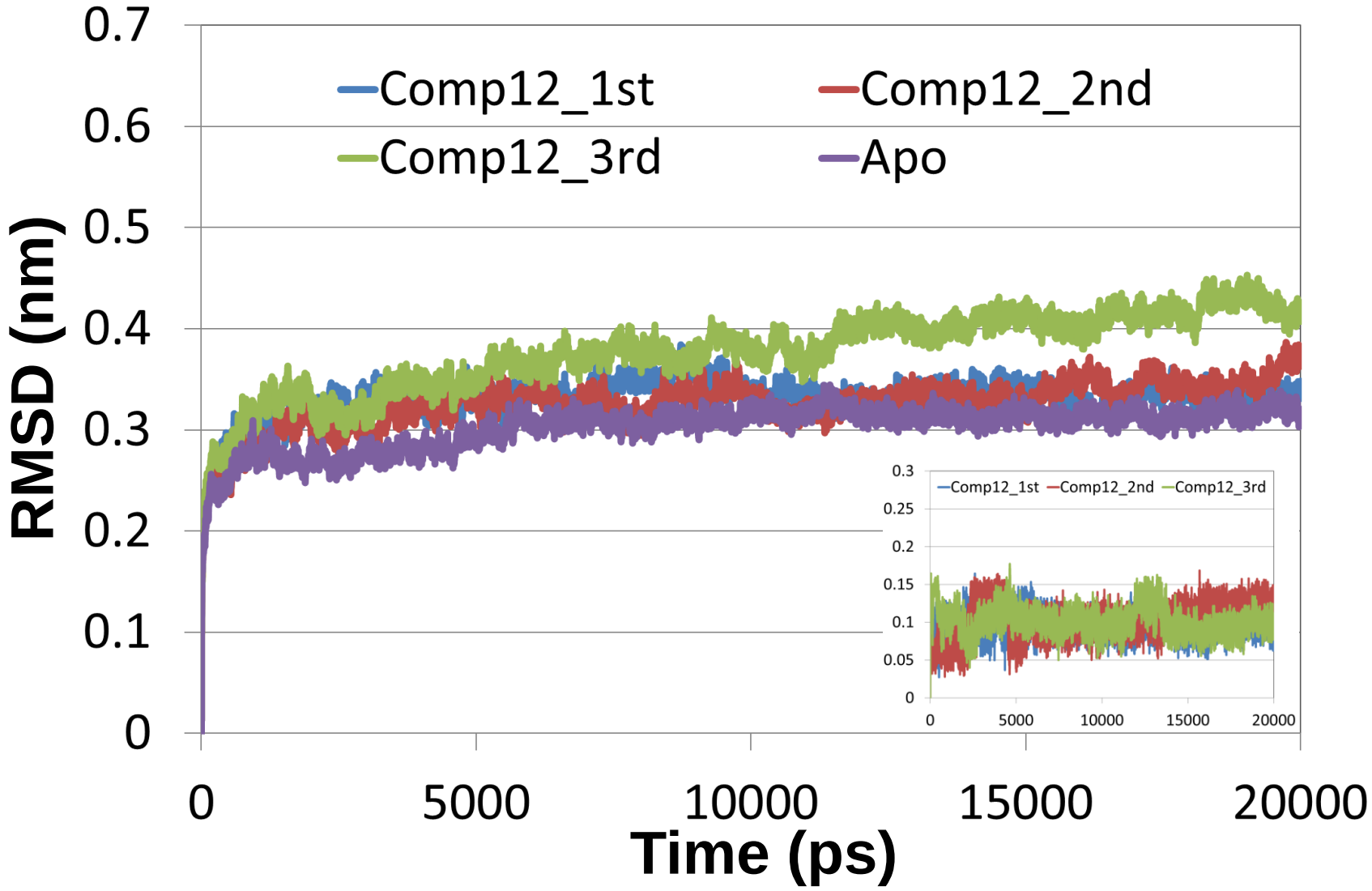
Radius of Gyration
g_gyrate -f md1.xtc -s md1.tpr -o gyrate.xvg

Potential Energy Measure
g_energy -f md1.edr -s md1.tpr -o energy.xvg
-> 10 0

Distance Measure
g_dist -f md1.xtc -s md1.tpr -n in_md1.ndx -o dist.xvg

H-bond Measure
g_hbond -f md1.xtc -s md1.tpr -n in_md1.ndx -num backbone_hbond.xvg
-> backbone to backbone

Molecular dynamics (MD) simulation result: System stability check using RMSD plots



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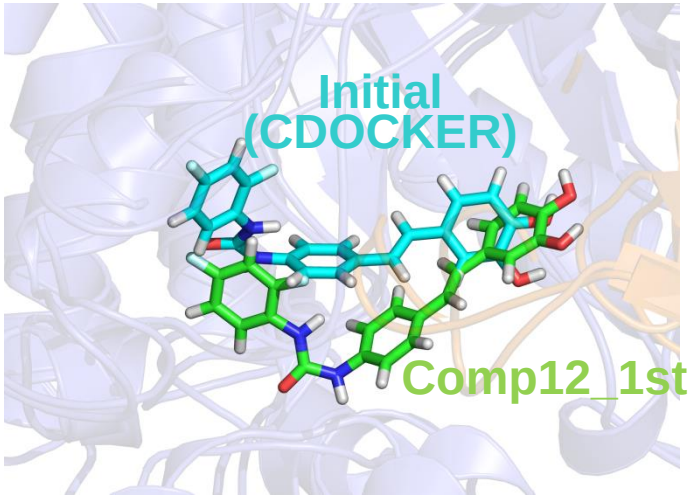
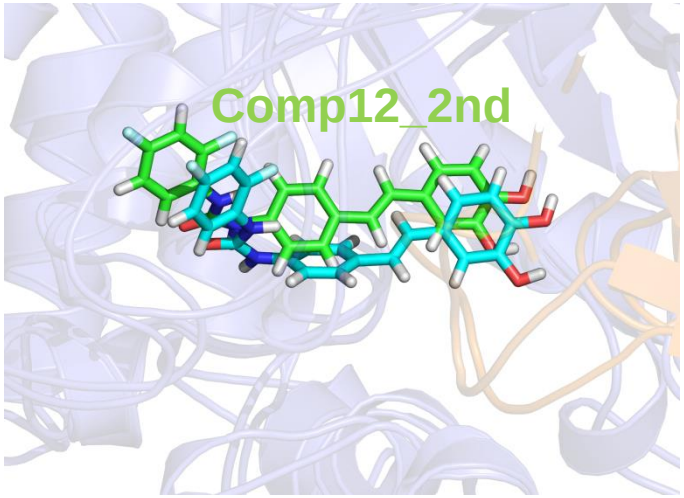
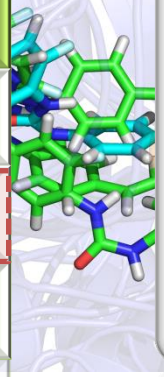
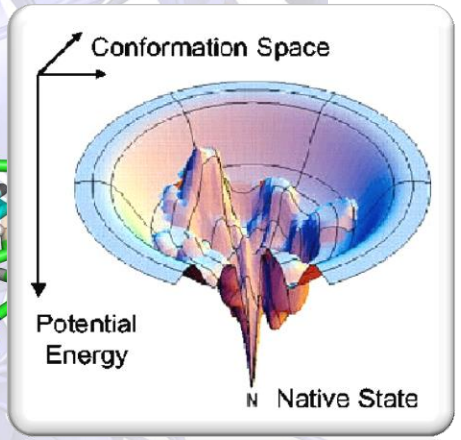
MD simulation result: binding modes of comp12 in representative structures





System	Interaction Energy (kJ/mol)	Van der Waals Energy (kJ/mol)	Electrostatic Energy (kJ/mol)
Comp12_1st	-235.876	-168.048	-67.8278
Comp12_2nd	-253.253	-202.956	-50.2964
Comp12_3rd	-203.842	-159.364	-44.4776





"2nd system was selected as the lowest interaction energy structure"

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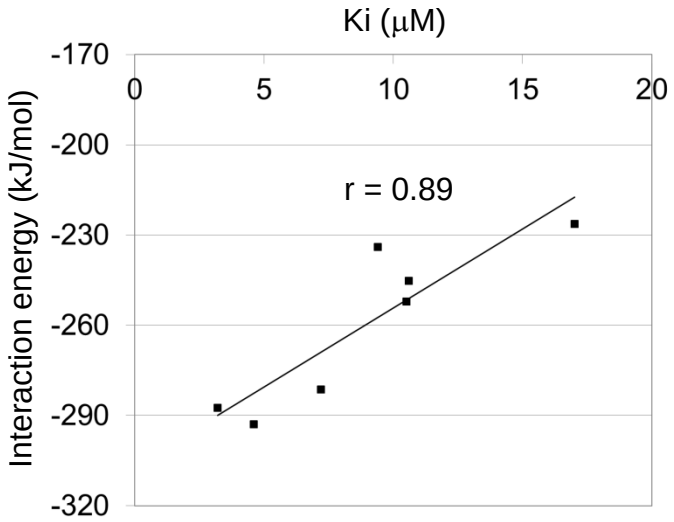
Validation of final binding site showing linearity between exp. Ki and calculated energy

To validate the final binding mode, exp. Ki values were correlated with calculated interaction energy

System	Experimental Ki (μM)	Interaction Energy (kJ/mol)
Comp6	10.6	-245.265
Comp7	10.5	-252.126
Comp11	7.2	-281.353
Comp12	3.2	-287.378
Comp13	4.6	-292.982
Comp14	17	-226.249
Comp16	9.4	-233.907

Correlation graph of exp. Ki values with interaction energy after 1.5 ns MDS



"After the 1.5 ns MDS, exp. Ki was well correlated with interaction energy"

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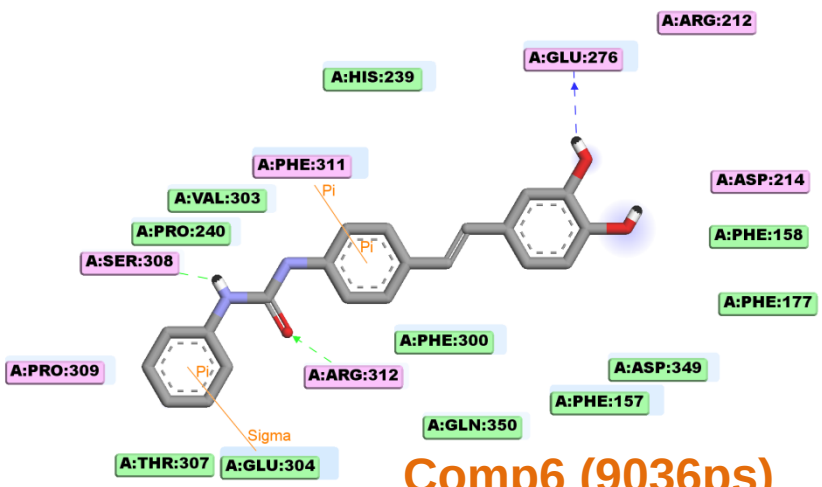
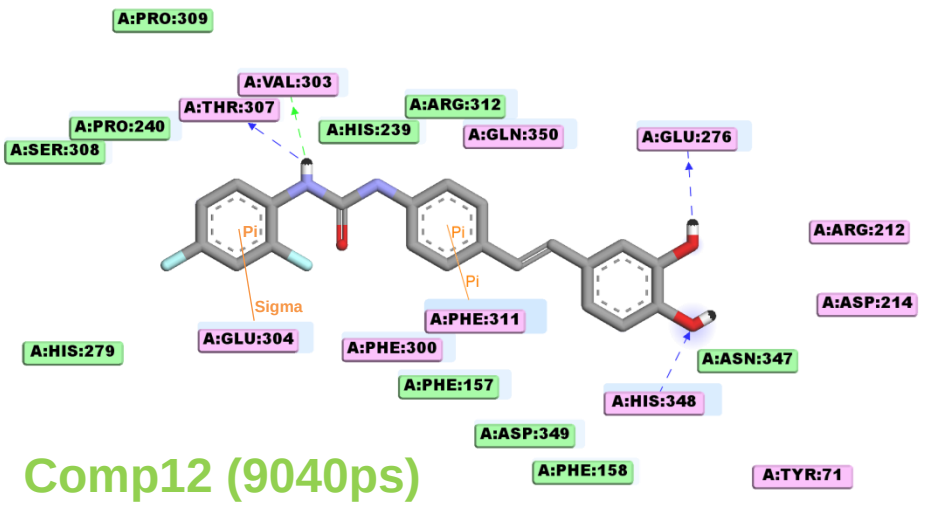
Binding mode comparison: 10ns MDS representative structures for Comp6 and Comp12 systems



Comp6 (9036ps)

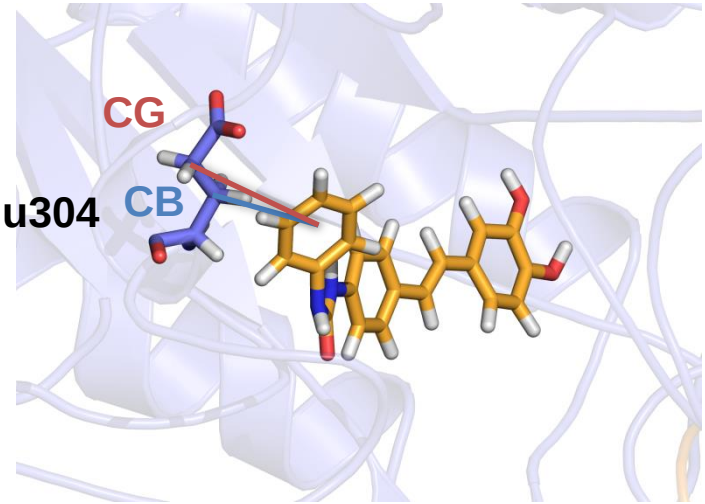


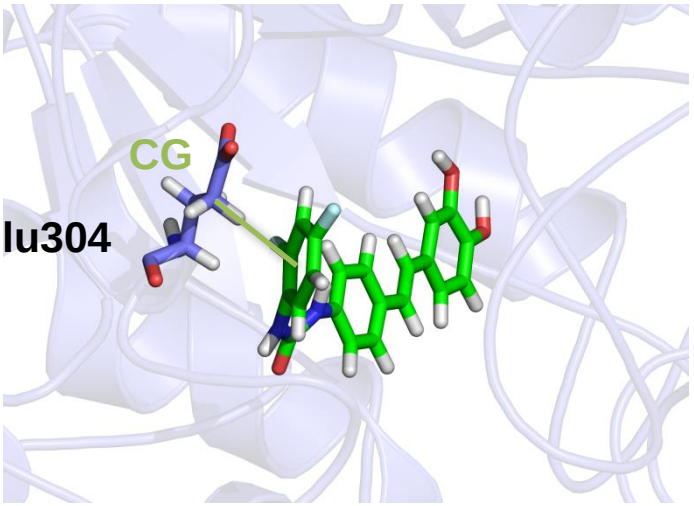
Comp12 (9040ps)

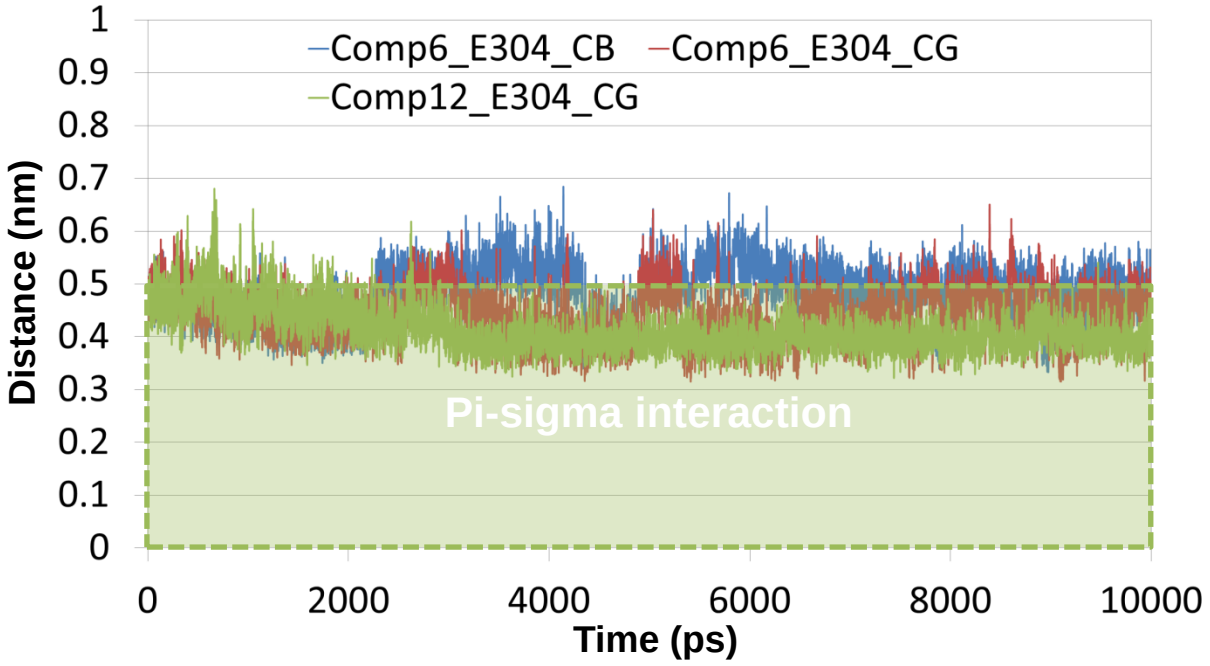
Ligand	Protein-ligand interactions		
	Hydrogen bonding residues (<3 Å)	Residues involved in charge or polar interaction	Hydrophobic contacting residues
Compound 6	**Glu276**, Ser308, Arg312	**Arg212**, **Asp214**, Pro309, **Phe311**	**Phe157**, **Phe158**, Phe177, **His239**, **Pro240**, Phe300, Val303, Glu304, Thr307, **Asp349**, Gln350
Compound 12	**Glu276**, Val303, Thr307, His348	Tyr71, **Arg212**, **Asp214**, Glu304, Phe300, **Phe311**, Gln350	**Phe157**, **Phe158**, **His239**, **Pro240**, His279, Ser308, Pro309, Arg312, Asn347, **Asp349**

Glu304 is charged interacting residue in comp12;
But, Glu304 is hydrophobic residue in comp6

Pi-sigma interaction comparison







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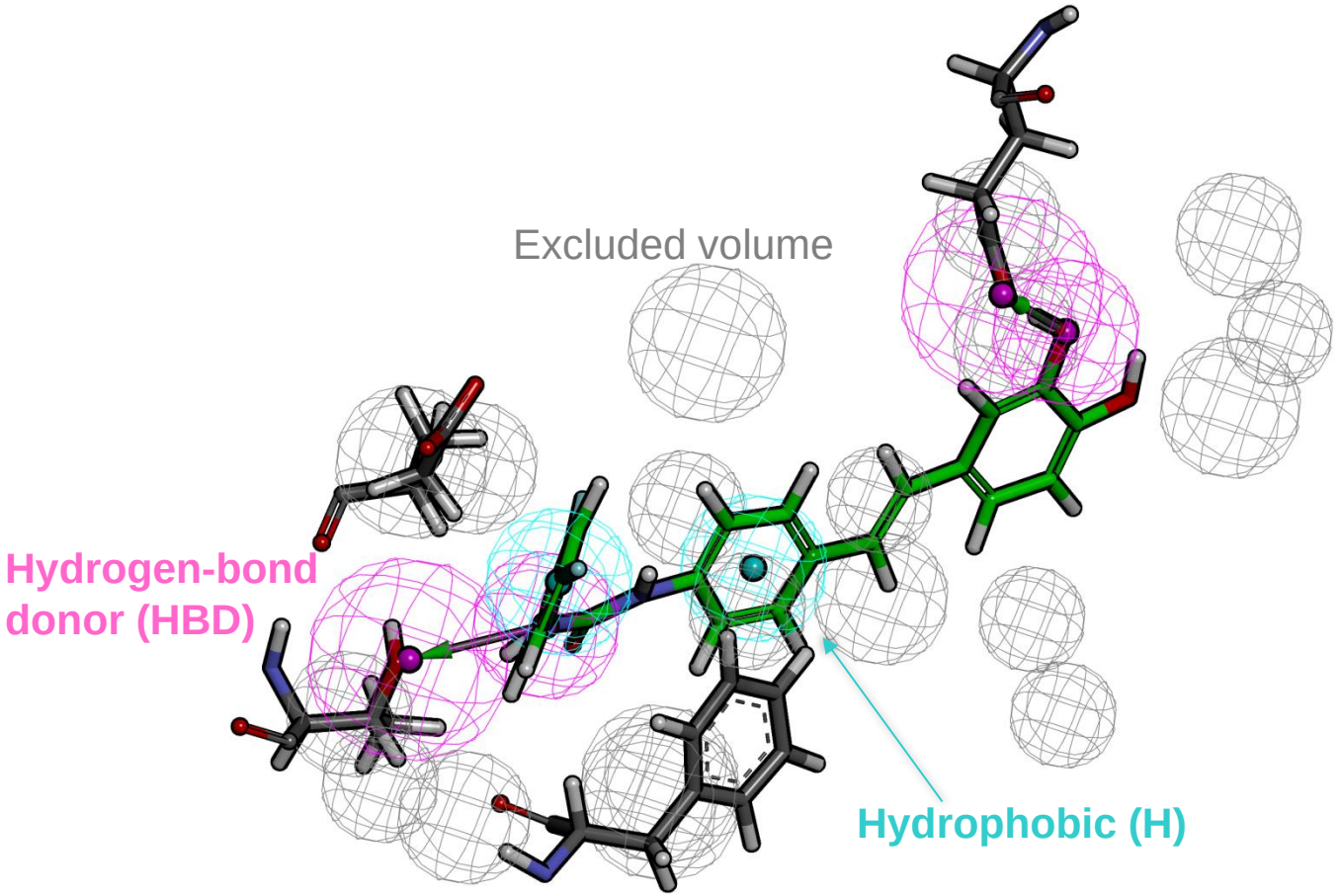
Generation of Receptor-ligand pharmacophore model

Based on the final structure, receptor-ligand phamacophore model was generated for the further virtual screening



Fit vale: 3.89

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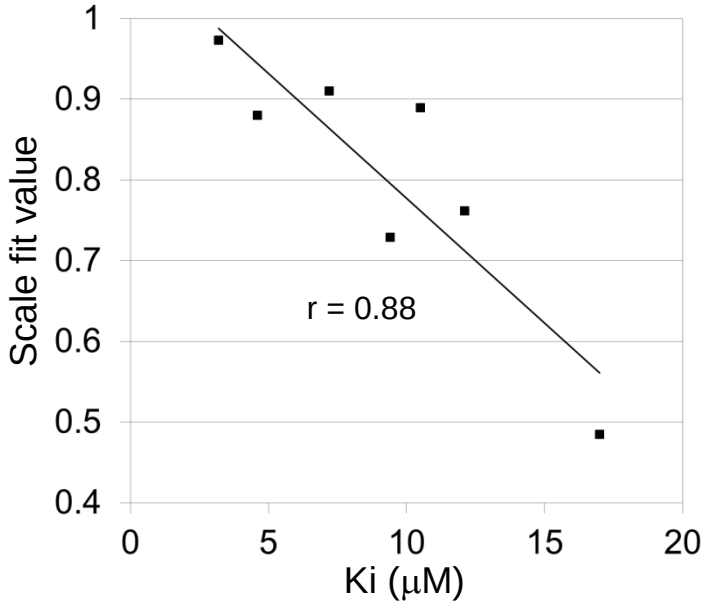
Validation of generated pharmacophore model showing linearity between exp. Ki and scale fit value

To validate the final binding mode, exp. Ki values were correlated with scale fit value

System	Time, ns	Exp. Ki (μM)	Scale fit value
Comp6	10	10.6	-
Comp7	1.5	10.5	0.89
Comp10	1.5	12.1	0.76
Comp11	1.5	7.2	0.91
Comp12	10	3.2	0.97
Comp13	1.5	4.6	0.88
Comp14	1.5	17	0.49
Comp16	1.5	9.4	0.73

Correlation graph of exp. Ki values with scale fit value after 1.5 ns MDS



"After the 1.5 ns MDS, exp. Ki was well correlated with scale fit value"

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Combined approach (*molecular docking and MD simulation*) to find out the reasonable binding mode

- ***To find out the reasonable binding modes of stilbene urea derivatives within active site of α-glucosidasese***

Homology modeling

3D structure of yeast α-glucosidasese was constructed using B. cereus oligo-1,6-glucosidase (PDB ID: 1UOK)

Molecular docking

Initial binding modes of stilbene urea derivatives were found within active site of α-glucosidasese

20 ns MD simulations (Adjustment)

The lowest energy structure (adjusted conformation of highest active compound) was selected

Molecular docking

The final docking poses within adjusted conformation of the best structure were obtained

2 ns MD simulation (Refinement)

The docked structures were refined by MDS

Receptor-ligand Pharmacophore generation

Finally, generation of phamacophore model for the further virtual screening

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References

- Books
  - Computer simulation of liquids by M. P. Allen & D. J. Tildesley.
  - Understanding Molecular Simulation by Daan Frenkel, Berend Smit
  - The Art of Molecular Dynamics Simulation by D. C. Rapaport.

- Popular simulation packages
  - GROMACS:
  - http://www.gromacs.org/
  - http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/
  - http://www.gromacs.org/@api/deki/files/198/=gmx-tutorial.pdf
  - http://md.chem.rug.nl/~mdcourse/index.html
  - CHARMM: http://www.charmm.org/
  - AMBER: http://ambermd.org/
  - NAMD: http://www.ks.uiuc.edu/Research/namd/

Thank you for your attention~*